Pre-emptive effect of multimodal analgesia in thoracic surgery

E. Doyle and G. M. R. Bowler

Summary

Thirty subjects undergoing posterolateral thoracotomy were allocated randomly to receive one of two analgesic regimens: group Pre received i.v. morphine, i.m. diclofenac and intercostal nerve blocks from T2 to T11, 20 min before operation and placebo injections after operation. Group Post received placebo injections before operation, and i.v. morphine, i.m. diclofenac and intercostal nerve blocks from T2 to T11 at the end of surgery, before discontinuation of anaesthesia. Visual analogue pain scores, extent and duration of intercostal nerve block, analgesic consumption and complications were assessed during the postoperative period by a single blinded observer. Subjects were followed-up for a minimum of 12 months to determine the incidence of post-thoracotomy pain syndrome. During the first 48 h after operation there were lower pain scores in group Pre when taking a vital capacity breath but there were no significant differences between the groups in any other measure. The effects of pre-emptive analgesia given before surgery appeared to be relatively modest in terms of analgesia, analgesic consumption and long-term outcome and were of limited clinical significance. (Br. J. Anaesth. 1998; 80: 147–151)

Keywords: analgesia, pre-emptive; surgery, thoracic; complications, post-thoracotomy syndrome

Evidence from basic research in mechanisms of pain suggests that administration of analgesic drugs may be more effective if given before, rather than after, a nociceptive stimulus. Some clinical work supports this concept when using local anaesthetic techniques, systemic opioids, extradural opioids, ketamine and combined or balanced analgesic regimens. Other studies have found little difference in the degree of postoperative pain or requirements for analgesics between groups where analgesics are administered after rather than before the start of surgery using opioids, local anaesthetics, non-steroidal anti-inflammatory drugs (NSAID) or combined techniques.

The proposed mechanism of this pre-emptive effect is that administration of analgesia before a nociceptive stimulus reduces the degree of sensitization produced in the nervous system by the stimulus and facilitates subsequent treatment. Noxious stimulation generates reflex hyperexcitability in the dorsal horn of the spinal cord. This central sensitization prolongs and increases sensitivity to noxious stimuli over an expanded receptive field (hyperalgesia), results in pain from normally innocuous stimuli (alldynia) and in spontaneous pain. Repetitive noxious stimuli evoke a progressively escalating response in the spinal cord which further magnifies the pain. An extension of this concept is that effective analgesia administered before a nociceptive stimulus may also reduce the risk of a postoperative chronic pain syndrome.

It is important to discriminate between the effects of pre-emptive analgesia where the same intervention is compared when given before or after the nociceptive stimulus, and preoperative analgesia where analgesia is given before surgery and compared with no intervention or with placebo. Administration of analgesia before surgery compared with no intervention or with placebo is known to provide superior analgesia and to reduce pain compared with placebo. The appropriate design of a study to detect the pre-emptive effects of an analgesic, if any, has been described and this study was performed in accordance with that design.

We designed this study to eliminate these factors by studying a major procedure associated with consistently high scores in measures of postoperative pain, adhering to the appropriate design for a study of pre-emptive analgesia and using a combined opioid, NSAID and local anaesthetic–analgesic regimen. We also studied the effect on postoperative chronic pain syndrome associated with thoracotomy to determine if the practice of pre-emptive analgesia had any effect on the incidence of this problem.

Patients and methods

The study was approved by the local Ethics Committee and informed written consent was obtained from each subject. We studied 30 subjects undergoing unilateral posterolateral thoracotomy for lobectomy or pneumonectomy. Exclusion criteria included any history of a chronic pain condition, current use of analgesic medications or contraindications to the use of non-steroidal anti-inflammatory drugs. Before operation, all subjects were instructed in the use of patient-controlled analgesia (PCA) and the use of a 100-mm visual analogue scale for reporting of pain, and introduced to the use of blunt tipped 27-gauge dental injection needles for determination of the extent of local anaesthetic block.

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Table 1  Patient data and operative procedures (mean (so or range) or number)

<table>
<thead>
<tr>
<th></th>
<th>Group Pre</th>
<th>Group Post</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>61.6 (34–79)</td>
<td>59.8 (30–72)</td>
</tr>
<tr>
<td>Procedure</td>
<td>Lobectomy: pneumonectomy: thoracotomy without lung resection</td>
<td>Lobectomy: pneumonectomy: thoracotomy without lung resection</td>
</tr>
<tr>
<td>Side (R:L)</td>
<td>6:9</td>
<td>8:7</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>119 (56)</td>
<td>95 (34)</td>
</tr>
<tr>
<td>Duration of postoperative chest drainage (h) (median (range))</td>
<td>48 (17–144)</td>
<td>42 (12–164)</td>
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</table>

Subjects were premedicated with temazepam 20 mg orally, 1–2 h before operation. Anaesthesia was induced after preoxygenation with propofol 2–3 mg kg\(^{-1}\) and atracurium 0.6 mg kg\(^{-1}\). After tracheal intubation with an appropriately sized double-lumen tube and verification of its position, the lungs were ventilated with 1–5% enflurane and nitrous oxide in oxygen, and an infusion of atracurium 0.5 mg kg\(^{-1}\) h\(^{-1}\) was commenced. The concentration of enflurane during surgery was varied as required to maintain heart rate and arterial pressure within 20% of pre-induction values. All surgical procedures were performed by the same surgeon in the morning of the same day of the week.

Subjects were allocated randomly using computerized randomization to one of two groups. In group Pre, subjects received morphine 10 mg i.v., diclofenac 75 mg i.m. and intercostal nerve blocks in spaces 2–11 with a total 40 ml of 0.5% bupivacaine with epinephrine 1/200 000 and 8.4% sodium bicarbonate 1 ml which has been shown to increase the duration of intercostal nerve block produced by bupivacaine and epinephrine.28 In group Post, subjects received dummy i.v. and i.m. injections and a series of dummy intercostal nerve blocks. No other analgesics were administered during surgery. The start of surgery was then delayed for at least 20 min after administration of analgesic or dummy injections to ensure that any analgesic intervention was effective before nociceptive stimulus.

At the end of surgery, subjects in group Pre received dummy i.v. and i.m. injections and a series of dummy intercostal nerve blocks. Subjects in group Post received morphine 10 mg i.v., diclofenac 75 mg i.m. and intercostal nerve blocks with a total of 40 ml of 0.5% bupivacaine with epinephrine 1/200 000 and 8.4% sodium bicarbonate 1 ml which has been shown to increase the duration of intercostal nerve block produced by bupivacaine and epinephrine. The two groups were similar in patient data and operative procedures (table 1).

Results

The two groups were similar in patient data and operative procedures (table 1). In all subjects there was an intercostal block from T2 to T11 on the side of surgery in the recovery area. One subject in group Pre and two in group Post required i.v. morphine in the recovery area. There was no difference between groups in postoperative consumption of morphine by patient-

mg h\(^{-1}\) and lockout interval 6 min. Diclofenac 50 mg orally was administered every 8 h. Additional boluses of morphine 5 mg were prescribed and administered by nursing staff if the visual analogue score was persistently greater than 40 mm. Intercostal nerve blocks were repeated by the same investigator as previously if a subject was in significant pain (visual analogue score > 40 mm), was unable to cough and clear secretions and had no demonstrable remaining intercostal nerve block. Physiotherapy and nursing care were given by the same people to patients in both groups.

Assessments of pain were performed in the recovery area and at 6, 12, 18, 24, 30, 42 and 48 h after operation. On these occasions subjects gave a visual analogue scale from 0–100 mm for pain before and after taking a vital capacity breath and the extent of the intercostal nerve block was assessed using a 27-gauge blunt tipped dental injection needle. Visceral frequency and arterial oxygen saturation were also noted at these times. Other assessments made were time to first oral intake and duration of chest drainage. All assessments were performed by a single observer who was unaware of the intraoperative analgesic management of the subjects.

After 48 h, PCA was discontinued and analgesia provided with dihydrocodeine 60 mg orally every 4 h as required, morphine 10 mg i.m. every 3 h as required and diclofenac 50 mg orally every 8 h as required. Analgesic consumption during the following week and duration of hospital stay were also noted.

At 6 and 12 months after operation, patients’ notes were examined to determine if they were still alive. If so a telephone call was made and subjects were asked about the occurrence of symptoms of post-thoracotomy pain or post-thoracotomy syndrome using the definition of the International Association for the Study of Pain29 of pain that recurs or persists along a thoracotomy scar at least 2 months after surgery. Specific questions were asked about a burning or aching quality to the discomfort, pain caused or worsened by routine stimuli or aching quality to the discomfort, pain caused or worsened by routine stimuli and delayed or exaggerated responses to routine stimuli. Current analgesic consumption for pain at the site of the thoracotomy was elicited. All of these calls were made by the same blinded observer.

We calculated that this study had a power of 80% to detect differences between groups which would be significant at the 5% level. This calculation was similar to that used in several other studies investigating the presence or absence of pre-emptive analgesia in clinically relevant circumstances.26 20  Statistical analysis was performed using the Student’s t test for normally distributed data and the Mann–Whitney U test for skewed data.
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controlled analgesia. Subjects in group Pre consumed a median of 92 (range 50–136) mg and those in group Post 82 (32–128) mg during the first 48 h after operation. Total morphine consumption comprising morphine by patient-controlled analgesia and additional boluses of 5 mg administered by nursing staff was 95 (50–156) mg in group Pre and 82 (32–172) mg in group Post.

There was no difference in visual analogue scores between patients at rest in group Pre and group Post at any of the assessments during the postoperative period (fig. 1).

In group Post, VAS scores during a vital capacity breath were significantly higher ($P < 0.05$) than those in group Pre at all assessments other than in the recovery area and at 6 h after operation (fig. 2). There was a consistent increase in VAS pain scores during a vital capacity breath over the first 36 h after operation in group Post but not in group Pre.

There was no difference between groups in duration of intercostal nerve block. Median duration of detectable block was 27 (range 8–42) h in group Pre and 24 (18–48) h in group Post. Two subjects in group Pre and three in group Post received repeat intercostal nerve injections on the day after surgery.

During the period from 48 h to 7 days after operation, there was no difference between groups in consumption of diclofenac, dihydrocodeine or morphine administered for pain (table 2).

There was no difference between groups in the time taken to first oral fluid intake, with a median of 9 (range 3–25) h in group Pre and 15 (4–22) h in group Post. There was no difference in the time of discharge from hospital (6 (5–14) days in group Pre and 6 (4–8) days in group Post). Two subjects in group Post were excluded from this analysis as they were transferred to other hospitals for management of a bleeding duodenal ulcer and for nursing care, respectively.

At telephone follow-up, two subjects in group Pre and none in group Post described symptoms of post-thoracotomy neuralgia. One subject in group Post was excluded from this analysis because he underwent subsequent lung transplantation.

Discussion

We have found an effect of pre-emptive analgesia on postoperative visual analogue pain scores during the 48 h after operation which was limited to a reduction in VAS pain scores during a vital capacity breath. There were no differences between groups in analgesic consumption, complications or long-term outcome, including the incidence of post-thoracotomy pain. This is despite the use of a model of severe postoperative pain, a design which fulfilled the requirements to detect any pre-emptive analgesic effect and a tightly controlled study design.

Thoracotomy is one of the most painful surgical procedures known, with multiple sources of nociception, including the surgical incision, disruption of ribs and intercostal nerves, pleural inflammation, pulmonary parenchymal damage and the presence of postoperative intercostal drains. The fact that all subjects received both preoperative and postoperative analgesics or placebo fulfils the requirement to detect a pre-emptive analgesic effect. All procedures involved posterolateral thoracotomy performed by the same surgeon while all analgesic interventions were performed by the same consultant anaesthetist and a single blinded observer performed all postoperative assessments to eliminate variability between observers. The similar timing of surgery in both groups implies that events which may have been influenced by ward routines, such as chest drain removal and hospital discharge, should have been influenced in the same way to a similar extent in both groups. The prolonged follow-up of these subjects is unique in studies of pre-emptive analgesia and was designed to detect any difference between groups in the incidence of post-thoracotomy neuralgia. Previous studies have suggested that the incidence and severity of chronic pain after surgery may be modified by the perioperative analgesic regimen\textsuperscript{25} but we were unable to find evidence to support this suggestion.

Various reasons why the work performed in animals is not consistently replicated in clinical practice have been suggested. In some of the studies

Table 2 Requirements for analgesia during postoperative days 2–7 in group Pre and group Post (median (range) number of doses)

<table>
<thead>
<tr>
<th></th>
<th>Group Pre</th>
<th>Group Post</th>
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</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>12 (1–19)</td>
<td>12 (6–16)</td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td>7 (1–16)</td>
<td>9 (3–17)</td>
</tr>
<tr>
<td>Morphine</td>
<td>0 (0–3)</td>
<td>1 (0–4)</td>
</tr>
</tbody>
</table>
which showed no effect, an appropriate pre-emptive study design was not used with analgesic premedication being administered or analgesic drugs being given before the surgical incision. The fact that subjects in this study did not undergo surgery until at least 20 min after the first set of injections and were kept anaesthetized for 20 min after the second set implies that subjects in group Pre had effective clinical analgesia at the start of surgery and subjects in group Post did not emerge from anaesthesia until their analgesic interventions were effective, although it may be that the NSAID component of the analgesic treatments requires more than 20 min to become fully effective.

Several studies have used as models relatively minor surgical procedures such as wisdom teeth extraction, which produce low intensity noxious stimuli that may not generate enough difference between pre-emptive and control groups to demonstrate a clinical effect. In addition, relatively minor surgery may not trigger the altered central processing of sensory inputs which causes subsequent hyperalgesia and allodynia. Conversely, the nociceptive stimulation which is produced during surgery with mixed cutaneous, visceral and muscular components, in addition to emotional or psychological factors, may be more difficult to prevent than that arising from the limited physical and chemical insults used in experimental animals. Clinical postoperative pain is a different entity from nociception inflicted during animal studies and it is not surprising that it is more difficult to demonstrate a genuine pre-emptive effect in this situation compared with animal models. Infusion analgesic regimes which are not titrated to patient request and which produce pain scores of zero may obscure any pre-emptive effect unlike on-demand analgesic regimes where analgesic consumption is determined by the patient and acts as an indicator of the degree of pain or nociception present.

Our analgesic management clearly failed to provide complete ablation of nociceptor stimuli during anaesthesia and surgery, as demonstrated by the requirement for analgesia in the recovery area in several patients, particularly for pain in the shoulder region out with the area of intercostal nerve block. These subjects were not excluded from the analysis because our intention was to compare a clinically relevant pre-emptive analgesic regimen with a clinically relevant non-pre-emptive analgesic regimen accepting that occasionally patients may not have complete analgesia on recovery from anaesthesia. This was despite intercostal nerve blocks, attempting to limit the production of inflammatory mediators with a systemic NSAID and suppressing the central perception of nociception with systemic opioid. Sympathetic and parasympathetic afferents would not have been blocked by our analgesic regimen and neither would the phrenic nerve, which is sensory to the pericardium, mediastinal and diaphragmatic pleura. This fact may also have served to obscure any pre-emptive analgesic effect in group Pre. It would only have been possible to ablate nociceptive stimuli completely in this group by using analgesic regimes which are not clinically relevant, such as very high extradural block or high-dose opioid which would both have presented problems of their own and necessitated postoperative ventilation. Alternatively, the use of interpleural analgesia may have produced a more widespread afferent block from the operated side.

The increase in VAS pain scores during a vital capacity breath in group Post but not in group Pre suggests that sensitization occurred in group Post either peripherally through inflammation, spinally or centrally. The absence of this increase in group Pre may be a manifestation of a pre-emptive analgesic effect.

In summary, this study adds to the growing body of evidence that the effects of pre-emptive analgesia given before surgery are relatively modest in terms of analgesia, analgesic consumption and long-term outcome, and are of limited clinical significance.

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References


